REMARKS

Claims 38-57 are pending in the above-identified application. The specification has been amended to correct mistranslations and typographical errors. A partial English translation of JP 2002-009951 is enclosed herewith in order to provide support for the correct translation of current pages 136-137 and 144. In view of the following remarks, Applicant respectfully requests that the Examiner withdraw all rejections and allow the currently pending claims.

Issues under 35 U.S.C. § 103(a)

1) The Examiner has rejected claims 38-41, 44-46, 49-52, and 54-57 under 35 U.S.C. § 103(a) as being unpatentable over Kunihiro et al. '028 (US 5,834,028) in view of Yui et al. '548 (EP 1029548).

2) The Examiner has rejected claims 38-41, 44-47, 49-52, and 54-57 under 35 U.S.C. § 103(a) as being unpatentable over Kunihiro et al. '028 in view of Yui et al. '548 and further in view of JP '790 (JP 11-171790).

3) The Examiner has rejected claims 38-41, 44-46, and 48-57 under 35 U.S.C. § 103(a) as being unpatentable over Kunihiro et al. '028 in view of Yui et al. '548 and further in view of Zushi '007 (US 5,574,007).

4) The Examiner has rejected claims 38-46, 49-52, and 54-57 under 35 U.S.C. § 103(a) as being unpatentable over Kunihiro et al. '028 in view of Yui et al. '548 and further in view of Klokkers-Bethke et al. '769 (US 5,335,769).

Applicant respectfully traverses. Reconsideration and withdrawal of these rejections are respectfully requested based on the following considerations.

Legal Standard for Determining Prima Facie Obviousness

MPEP 2141 sets forth the guidelines in determining obviousness. First, the Examiner has to take into account the factual inquiries set forth in *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966), which has provided the controlling framework for an obviousness analysis. The four *Graham* factors are:

(a) determining the scope and content of the prior art;

(b) ascertaining the differences between the prior art and the claims in issue;

(c) resolving the level of ordinary skill in the pertinent art; and

(d) evaluating any evidence of secondary considerations.

Graham v. John Deere, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966).

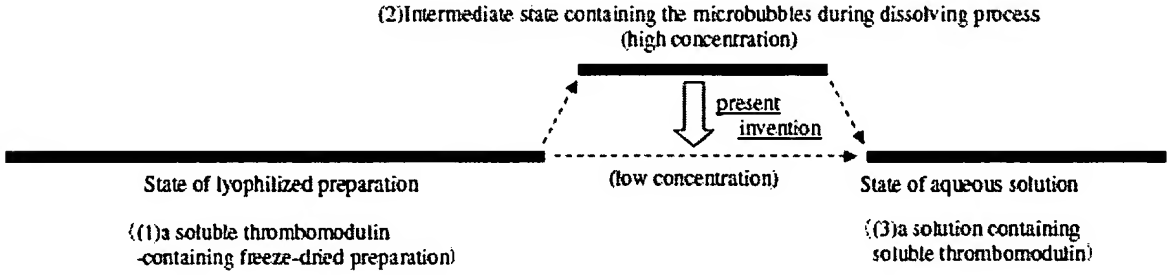
Second, the Examiner has to provide some rationale for determining obviousness. MPEP 2143 sets forth some rationales that were established in the recent decision of *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385 (U.S. 2007).

As the MPEP directs, all claim limitations must be considered in view of the cited prior art in order to establish a *prima facie* case of obviousness. *See* MPEP 2143.03.

The Present Invention and its Advantages

The present invention prevents the formation of microbubbles in the aqueous thrombomodulin (TM) solution. These microbubbles form cloudiness in the solution that is maintained for a long period of time and causes a problem of inappropriateness of immediate injection of the solution (page 5 of the present specification).

The present invention has two aspects: (i) the process of dissolution and (ii) a high concentration of TM. In the present invention, the aqueous medium is added to a lyophilized preparation of TM that gives a state of microbubble formation. A high concentration of TM generates the microbubbles.



The above process of dissolution (i) includes the step of preparing a solution containing soluble TM (the state of (3) in the above scheme) from a lyophilized soluble TM preparation (the state of (1)), and the high concentration of TM (ii) is a concentration of 10 mg/mL or higher, in which a resulting solution obtained by the addition of an aqueous medium for dissolution gives cloudiness due to microbubbles formed during the dissolving process. The present invention successfully overcomes this problem by the addition of a surfactant. When a TM solution is prepared in the same manner but has a final concentration of 5 mg/mL, the above intermediate state is not observed, and the dissolution of TM in an aqueous medium occurs very rapidly to give a complete dissolution of TM without formation of microbubbles and the resulting cloudiness.

In other words, the formation of the microbubbles during the dissolving process only occurs when the concentration of TM is as high as approximately 10 mg/mL at final concentration. This problem was not known before the filing of the present invention, and the present invention successfully achieved a method to prevent the formation of the microbubbles and the resulting cloudiness at a high concentration of TM by using the surfactant as defined in the pending claims.

Distinctions over the Cited References

Kunihiro et al. '028 disclose, for example in Example 12, the step of dissolving lyophilized soluble TM as a raw material (i.e., not in a form of a pharmaceutical preparation) in distilled water for injection together with several pharmaceutical carriers and the step of successive lyophilization. However, Kunihiro et al. '028 fail to disclose a solution used for dissolution of a lyophilized preparation containing a soluble TM together with pharmaceutical additives other than TM. Kunihiro et al. '028 also fail to disclose a solution obtained by dissolving the lyophilized preparation containing a soluble TM. Accordingly, a concentration of TM solution prepared by dissolving a lyophilized product obtained in the lyophilization process is unknown from the disclosure in Kunihiro et al. '028. Thus, Kunihiro et al. '028 fail to disclose any specific process of dissolving a pharmaceutical product of lyophilized soluble TM in a dissolving medium to obtain an injectable solution of TM at a given concentration.

Further, based on the entire disclosure of the reference, a solution containing the soluble TM, obtained by dissolving the lyophilized preparation of the soluble TM by using the solution for dissolution, has a low concentration of TM (about 5 mg/mL) and not a high concentration near 10 mg/mL. Therefore, the problem of cloudiness was not caused in Example 12 of Kunihiro et al. '028.

Moreover, the purpose of using a surfactant in Kunihiro et al. '028 is to prevent absorption of TM to a surface of a container at a very low concentration of TM, i.e., approximately 0.003 mg titer/mL (col. 5, lines 1-15, Experiments 4-5). Kunihiro et al. '028 fail to disclose that a higher concentration of TM is applied, and therefore, one of ordinary skill in the art would not have been motivated in view of Kunihiro et al. '028 to choose a much higher concentration of TM.

Yui et al. '548 disclose a solution containing soluble TM. However, Yui et al. '548 do not disclose a process of lyophilizing the disclosed solution of TM or a process of redissolving the resulting freeze-dried TM by addition of an aqueous medium. Furthermore, the Yui et al. '548 reference is irrelevant to the present invention because Yui et al. '548 lack any disclosure of the process of dissolving the lyophilized preparation of a soluble TM. Therefore, Yui et al. '548 lack any disclosure of the intermediate state (2) in the dissolution of high concentrate TM as shown in the above scheme as well as any disclosure of the state of lyophilized preparation (1). As such, Yui et al. '548 fail to disclose dissolving a lyophilized soluble TM preparation so as to obtain a solution of TM at a high concentration of 10 mg/mL.

Furthermore, the Yui et al. '548 reference is completely silent about a process of lyophilization or a resulting lyophilized pharmaceutical product. In paragraph [0007], Yui et al. '548 disclose, "Meanwhile, it had been discovered that, in the process of freeze-drying of a thrombomodulin-containing aqueous solution, a part of thrombomodulin is converted, though in a minute amount, into a polymeric matter due to a denaturization to form a polymer in which several molecules of thrombomodulin are held in association." This description means that Yui et al. '548 provide an injectable solution to solve problems in the lyophilizing process of conventional methods and also means that the preparation of an injectable solution without using a lyophilization process is a feature of Yui et al. '548.

In other words, the Yui et al. '548 reference is silent about a lyophilizing process and also implicitly discloses that lyophilization should be avoided or prohibited. Therefore, the Yui et al. '548 reference is totally irrelevant to a process of dissolution of a lyophilized product or any problem accompanied with the process of dissolving a lyophilized product (i.e., a problem of the formation of microbubbles to be solved by the present invention). Furthermore, one of ordinary skill in the art would have no reason or rationale to combine Kunihiro et al. '028, which disclose a lyophilized pharmaceutical product of TM, with Yui et al. '548, which disclose that a lyophilization process of TM should be avoided or prohibited.

To establish a *prima facie* case of obviousness of a claimed invention, all of the claim limitations must be disclosed by the cited references. As discussed above, Kunihiro et al. '028 fail to disclose all of the claim limitations of independent claims 38 and 56-57, and those claims dependent thereon. Applicant respectfully submits that the other cited references fail to overcome these deficiencies. Accordingly, the combination of references does not render the present invention obvious.

Applicant respectfully submits that the Examiner has failed to make a *prima facie* case of obviousness for these further reasons. First, the invention must be considered as a whole. (MPEP 2141.02(I)). It is improper for the Examiner to take parts from several pieces of prior art and combine them in a piecewise manner for the purposes of anticipating or rendering obvious the present invention. As recited in MPEP 2141.02, the claimed invention as a whole must be considered rather than selecting specific elements from a multitude of prior art in order to come to Applicant's claimed invention.

Second, Applicant contends that the Examiner has indulged in impermissible hindsight in making the obviousness rejection. That is, the outstanding Office Action merely reflects the piecewise combination of various elements of various patents, which directly contradicts the rationale of MPEP 2143.01 that the "fact that the claimed invention is within the capabilities of one of ordinary skill in the art is not sufficient by itself to establish *prima facie* obviousness."

Both Kunihiro et al. '028 and Yui et al. '548 disclose a pharmaceutical composition that does not contain a surfactant as well as a pharmaceutical composition containing a surfactant. More specifically, Kunihiro et al. '028 mainly relate to the addition of arginine, which can be used regardless of the addition of a surfactant, as recited in claim 1. Furthermore, Yui et al. '548 disclose an embodiment to achieve stability by reducing a volume of gaseous space in a container. Accordingly, the Examiner's rejections are made by the combination of arbitrary embodiments chosen from Kunihiro et al. '028 and Yui et al. '548 after recognition of the present invention.

Furthermore, as the Examiner admits, Kunihiro et al. '028 fail to disclose the limitation "a solution containing soluble thrombomodulin...at a concentration of 10 mg/mL or higher" as recited in independent claims 38 and 56-57. The Examiner relies on Yui et al. '548 to overcome this deficiency.

Yui et al. '548 disclose, "While the upper limit of the thrombomodulin content is not specifically restricted, a concentration of thrombomodulin of, for example, not more than 15 mg, preferably not more than 10 mg, especially preferably not more than 6 mg, per 1 ml may be exemplified" (page 9, lines 31-33). Although Yui et al. '548 state that the upper limit of the thrombomodulin content is not specifically restricted, the reference does provide preferred upper limits and the examples never provide a content above 6 mg/mL. In addition, Yui et al. '548 only disclose the concentration of the solution of TM which is prepared not by the process of dissolving the lyophilized preparation of a soluble TM. The fact that Yui et al. '548 do not absolutely disclose the concentration of the solution of TM which is prepared by the process of dissolving the lyophilized preparation of a soluble TM is very important and must be taken into consideration.

Previously, Applicant provided statements regarding the problem of the formation of cloudiness as a result of micro-bubble foaming, which was caused by thrombomodulin content being 10 mg/mL or higher. The Examiner was not persuaded by this argument. Applicant provides additional remarks and case law herein to show that one of ordinary skill in the art would not have arrived at the claimed method in view of the cited references.

The discovery of the problem is relevant to patentability. Applicant respectfully submits that the discovery of the source of the problem would have been unobvious to one of ordinary skill in the art. When making an assertion of obviousness, it is insufficient to argue that "the source of the problem would have been discovered." *In re Peehs*, 612 F.2d 1287, 204 USPQ 835, 837 (CCPA 1980). If a "problem" is not recognized, a solution to the unrecognized problem could not have been *prima facie* obvious. *In re Sponnoble*, 405 F.2d 578, 160 USPQ 237 (CCPA 1969) and *Ex parte Campbell*, 211 USPQ 575 (Bd. App. 1981). According to MPEP 2141.02(III), a patentable invention may lie in the discovery of the source of a problem even though the remedy may be obvious once the source of the problem is identified. This is part of the "subject matter as a whole" which should always be considered in determining the obviousness of an invention under 35 U.S.C. § 103. Specifically, both Kunihiro et al. '028 and Yui et al. '548 fail to disclose the problem to be solved by the present invention (i.e., the problem of cloudiness caused by microbubbles generated at the time of the dissolution of a TM lyophilized preparation at the high concentration of 10 mg/mL or more.

As previously mentioned, Kunihiro et al. '028 fail to disclose a process of dissolving a lyophilized pharmaceutical product of a soluble TM in a given volume of distilled water. However, even if the Examiner might possibly interpret that Kunihiro et al. '028 implicitly suggest a solution of TM at a concentration of 5 mg/mL, Kunihiro et al. '028 do not disclose a concentration above 5 mg/mL. Further, Yui et al. '548 do not provide any examples with a concentration above 6 mg/mL. Therefore, these references individually and collectively suggest low concentrations of thrombomodulin, i.e. concentrations at or below 5-6 mg/mL. In view of these teachings, the references "teach away" from the claimed invention, and therefore, no *prima facie* case of obviousness is established.

In *Ex parte Whalen*, 89 USPQ2d 1078, 1082 (Bd. Pat. App. & Int. 2008), which was decided by an expanded panel of the Board after *KSR*, the Board of Appeals noted, "The Examiner finds that '[a]lthough Evans does not specifically recite the instantly claimed viscosity of 150 cSt at 40°C..., Examiner takes the position that compositions disclosed by Evans inherently possess the same viscosity...as the instantly claimed invention, because Evans'

compositions comprise similar component[s] used in overlapping ranges of concentrations.'" The Board of Appeals held:

> The Examiner has not made out a prima facie case that the claimed compositions would have been obvious based on the teachings of Evans, Greff '767, or Taki. While "the discovery of an optimum value of a variable in a known process is normally obvious," *In re Antonie*, 559 F.2d 618, 620 [195 USPQ 6] (CCPA 1977), this is not always the case. One exception to the rule is where the parameter optimized was not recognized in the prior art as one that would affect the results. *Id.*

Id. at 1083. The Board of Appeals specifically highlighted that "the references all suggest that low viscosity was a desired property in embolic compositions." *Id.* at 1084.

Similarly, in the outstanding Office Action, the Examiner argues that the limitations regarding the prevention and/or inhibition of microbubbles caused by thrombomodulin content being 10 mg/mL or higher would be inherent to the cited references. However, both Kunihiro et al. '028 and Yui et al. '548 suggest low concentrations of thrombomodulin, i.e. concentrations at or below 5-6 mg/mL. Furthermore, Kunihiro et al. '028 and Yui et al. '548 do not even recognize the problem of the formation of cloudiness as a result of micro-bubble foaming, which was caused by thrombomodulin content being 10 mg/mL or higher. As such, it would not be obvious to select a thrombomodulin content of 10 mg/mL or higher.

It must be emphasized that both Kunihiro et al. '028 and Yui et al. '548 totally fail to disclose the problem of the formation of cloudiness which is caused by the lyophilized preparation of thrombomodulin at a concentration of 10 mg/mL or higher. In other words, the problem was not known before the present invention was made, and the inventor of the present invention first found and solved the problem. In addition, the solution disclosed in the cited references do not have the problem of cloudiness. In contrast, the present invention has an advantageous effect of eliminating the cloudiness, which was an unknown problem in the field of art before the present invention was made.

In this regard, the examples and comparative examples of the present specification show that Kunihiro et al. '028 and Yui et al. '548 do not prevent or inhibit microbubbles caused by thrombomodulin content being 10 mg/mL or higher. Table 5 on pages 143-147 of the present

specification provides the conditions and results of the relevant examples. The table below summarizes these relevant examples. The present specification provides further details.

	Composition	Addition amount (mg)	Dissolving aqueous solution	Silicone coating	Pressure reduction degree	Transmittance (%)
Example 2-2-1	TMD123H Polysorbate 80	10 0.01	distilled water	uncoated vial	-	99.5
Comparative Example 2-1	TMD123H	10	distilled water	uncoated vial	-	90.5
Example 2-1-1	TMD123H Polysorbate 80	30 0.1	distilled water	uncoated vial	-	99.5
Comparative Example 2-3-1	TMD123H	30	distilled water	uncoated vial	-	79.7

The Examiner is respectfully requested to review the above table as it provides strong evidence of the patentability of the present invention. Specifically, when comparing inventive Example 2-2-1 and Comparative Example 2-1 wherein the thrombomodulin content is 10 mg/mL, the only difference in the conditions is the inclusion of Polysorbate 80 in the inventive example. Similarly, when comparing inventive Example 2-1-1 and Comparative Example 2-3-1 wherein the thrombomodulin content is 30 mg/mL, the only difference in the conditions is the inclusion of Polysorbate 80 in the inventive example. However, the present invention is unexpectedly superior when comparing transmittance in both cases. In other words, the higher transmittance means less microbubbles and less cloudiness. When comparing 10 mg/mL of thrombomodulin versus 30 mg/mL of thromobomodulin, the present invention maintains the same high transmittance, but the comparative examples produce an even lower transmittance. Thus, these examples strongly evidence that the cited references do not produce the results of the present invention.

As further evidence, enclosed herewith is a 37 CFR § 1.132 Declaration of Fumihide Nishio, the present inventor. The Examiner is respectfully requested to review the enclosed Declaration.

In the enclosed Declaration, three samples were prepared to show that the problem of cloudiness is solved by the present invention and that the cited references do not have the problem of cloudiness. During the interview on December 15, 2009, the Examiner requested an explanation of the advantages and unexpected results of the present invention. In this regard, the Rule 132 Declaration states:

> When a lyophilized preparation is dissolved to obtain a solution for injection, microbubbles are generated in the comparative example, not containing a surfactant, during the dissolution process to obtain a solution at a high TM concentration, i.e., as high as 10 mg/mL or more. Due to this problem, some period of time is required before a clear injectable solution is obtained, which delays the start of administration by injection. In contrast, by using the lyophilized preparation containing a surfactant according to the present invention, rapid preparation of a clear TM solution at a concentration of 10 mg/mL or higher is achievable so that administration can be promptly conducted without delay.

Relevant to this § 103(a) rejection, *Graham v. John Deere*, 383 U.S. 1, 17, 148 USPQ 459, 467 (1966) has provided the controlling framework for an obviousness analysis, wherein a proper analysis under § 103(a) requires consideration of the four *Graham* factors. One such factor includes the evaluation of any evidence of secondary considerations (e.g., commercial success; unexpected results). 383 U.S. at 17, 148 USPQ at 467. In this regard, Applicant respectfully submits that the present invention has achieved unexpected results, whereby such results rebut any asserted *prima facie* case of obviousness. *See In re Corkill*, 711 F.2d 1496, 226 USPQ 1005 (Fed. Cir. 1985). *See* MPEP 716.02(b) and 716.02(e).

According to MPEP 2145, rebuttal evidence and arguments can be presented in the specification or by way of a declaration under 37 CFR 1.132, *In re Soni*, 54 F.3d 746, 750, 34 USPQ2d 1684, 1687 (Fed. Cir. 1995). Office personnel should consider all rebuttal arguments and evidence presented by Applicant. See, e.g., *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687 (error not to consider evidence presented in the specification). Rebuttal evidence may also include evidence that the claimed invention yields unexpectedly improved properties or properties not present in the prior art. Rebuttal evidence may consist of a showing that the claimed compound possesses unexpected properties. *In re Dillon*, 919 F.2d 688, 692-93, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990).

As stated in *KSR International Co. v Teleflex Inc.*, 82 USPQ2d 1385, 1396 (2007), "rejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." Furthermore, the mere fact that references ***can*** be combined or modified does not render the resultant combination obvious unless the results would have been predictable to one of ordinary skill in the art. *Id.* As described above, Applicant has shown that the present invention achieves unexpected and unpredictable results. Reconsideration and withdrawal of this rejection are respectfully requested for this reason.

Moreover, according to MPEP 2143.01, the combination of references cannot change the principle of operation of the primary reference or render the reference inoperable for its intended purpose. As discussed above, Yui et al. '548 disclose that lyophilization should be avoided or prohibited. Thus, Yui et al. '548 cannot be properly combined with Kunihiro et al. '028, which disclose the step of dissolving lyophilized soluble TM as a raw material in distilled water for injection together with several pharmaceutical carriers and the step of successive lyophilization. In fact, Yui et al. '548 actually teach away from the lyophilization recited in Kunihiro et al. '028. Therefore, a *prima facie* case of obviousness has not been established, and withdrawal of the outstanding rejections is respectfully requested.

As discussed above, Kunihiro et al. '028 and Yui et al. '548 do not disclose each and every aspect of claims 38 and 56-57, from which all other pending claims ultimately depend. Applicant respectfully submits that the other cited references do not overcome the deficiencies of this reference.

The cited references or the knowledge in the art provide no reason or rationale that would allow one of ordinary skill in the art to arrive at the present invention as claimed. Therefore, a *prima facie* case of obviousness has not been established, and withdrawal of the outstanding rejections is respectfully requested. Any contentions of the USPTO to the contrary must be reconsidered at present.

CONCLUSION

A full and complete response has been made to all issues as cited in the Office Action. Applicant has taken substantial steps in efforts to advance prosecution of the present application. Thus, Applicant respectfully requests that a timely Notice of Allowance issue for the present case clearly indicating that each of claims 38-57 are allowed and patentable under the provisions of title 35 of the United States Code.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Chad M. Rink, Reg. No. 58,258, at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

By _____ #42,874

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Attachment: 37 CFR § 1.132 Declaration of Fumihide Nishio
partial English translation of JP 2002-009951

CMR

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